Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis at Universitas Academic Hospital: A 4-year Review

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I, Fatima Moosa, declare that the coursework Masters Degree mini-dissertation that I herewith submit in publishable manuscript format towards the Master of Medicine qualification, MMed (Dermatology) at the University of the Free State, is my independent work, and that I have not previously submitted this work for a qualification at this or another institution of higher education.

Abstract

Background

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but life-threatening dermatologic conditions that are part of the same disease spectrum. Drugs are the main inciting factor of this delayed (type IV) hypersensitivity reaction which produces epidermal and mucosal detachment. Despite morbidity and mortality being high, there are limited data available on SJS and TEN in South Africa. The objective of this study was to characterise patient demographics, aetiology and implicated drugs, treatment, and outcome in patients with SJS and TEN at a tertiary academic hospital in the Free State, South Africa.

Methods

A retrospective, cross-sectional descriptive single centre study which included participants managed at Universitas Academic Hospital, South Africa between 2016 and 2020 was performed.

Results

Fifty-five cases meeting the inclusion and exclusion criteria were included in this study. The cohort comprised TEN, SJS-TEN and SJS (n=40, n=10 and n=5 respectively). The mean age of the cohort was 37-years (range: 21- 67). Seventy percent were HIV-infected. Antibiotics (58%) and antiretroviral therapy (30%) were the most common drug classes implicated, with trimethoprim-sulfamethoxazole (22%) and nevirapine (16%) being identified as the most commonly implicated drugs. The major complication in the cohort was sepsis (42%). Supportive care formed the mainstay of treatment and the mortality rate was 14.5%.

Conclusion

The majority of the patients in this cohort were HIV infected, with antiretroviral therapy (specifically nevirapine) and antibiotics (specifically trimethoprim-sulfamethoxazole, used for prophylaxis of Pneumocystis jirovecii pneumonia (PCP) in the HIV-infected population) being commonly implicated causes of SJS and TEN. In resource-limited settings such as our facility, supportive care forms the predominant mode of treatment with a relatively good outcome.

Keywords

Cutaneous adverse drug reaction

Hypersensitivity reaction

South Africa

Stevens-Johnson syndrome

Toxic Epidermal Necrolysis

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Abbreviations

AKI	Acute kidney injury
ALDEN	Algorithm of drug causality for epidermal necrolysis
ARDS	Acute respiratory distress syndrome
ART	Antiretroviral therapy
CD4/CD8/CD25	Cluster of differentiation 4/8/25
EFV	Efavirenz
EM	Erythema multiforme
ETC	Emtricitabine
ETH	Ethambutol
Hb	Haemoglobin
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSREC	Health science research and ethics committee
ICU	Intensive Care Unit
INH	Isoniazid
IVIg	intravenous immunoglobulin
NHLS	National health laboratory service
NSAIDs	Nonsteroidal anti-inflammatory drugs
NVP	Nevirapine
PCP	Pneumocystis jirovecii pneumonia
PZA	Pyrazinamide
RH	Rifampicin
SAS	System Analysis Software
SCAR	Severe Cutaneous Adverse Reaction
SCORTEN	Score of Toxic Epidermal Necrolysis
SJS	Stevens-Johnson syndrome
SLE	Systemic lupus erythematosus
TBSA	Total body surface area
TDF	Tenofovir
TEN	Toxic epidermal necrolysis
TMP-SMX	Trimethoprim-sulfamethaxozole
TNF-A	Tumour necrosis factor-alpha
UAH	Universitas Academic Hospital
VL	Viral load
VTE	Venous thromboembolism
WHO	World Health Organization

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Chapter 1

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are regarded as rare, life-threatening subtypes of severe cutaneous adverse reactions (SCARs). These immune -mediated reactions are mostly induced by drugs and less commonly secondary to some infections. Initially, there is a prodrome of flu-like symptoms with subsequent development of painful, dusky, violaceous skin macules which progress to epidermal necrosis culminating in full-thickness denudation.[1]

Stevens-Johnson syndrome and TEN are considered to be part of the same spectrum of disease and are clinically differentiated into three categories based on the total body surface area (TBSA) involved. By definition, SJS encompasses skin detachment of 10% or less, SJS-TEN overlap between 10% - 30% and TEN more than 30% of the body surface area, with all three categories requiring mucosal involvement for clinical diagnosis.[1] In this article, the abbreviation SJS and TEN will be used to refer to all three categories.

Epidemiology

The worldwide incidence of SJS and TEN is estimated at approximately 1-6 cases per million persons per year and 0.4-1.2 cases per million persons per year respectively.[1,2] The generalisability of this is problematic as it is not necessarily reflective of developing countries, as most of these epidemiological studies have been conducted on European cohorts, with a scarcity of studies in the developing world, specifically Africa.[3] The prevalence and incidence differ substantially between countries and is contingent on various factors such as different population groups with varying genetic predispositions.[4,5]

A study conducted in the United States estimated the incidence of SJS and TEN to be 9.2 per million adults per year and 1.9 per million adults per year respectively from 2009-2012.[6] Frey *et al.* calculated an incidence rate of 5.76 per million persons per year of SJS and TEN cases between 1995-2013, which included paediatric cases.[2] Comparatively, the existing literature shows that no country-wide studies have been performed to investigate epidemiology and outcome of patients with SJS and TEN in South Africa. Furthermore, the sparse studies that have been conducted in South Africa are not comparable as they have had different study designs.[7-9] Further research would contribute to the available data and pharmaco-vigilance, also possibly identifying areas of uncertainty that need more investigation.

Pathophysiology

Recently, there has been extensive research on the pathogenesis of SJS and TEN, which has resulted in significant progress in understanding the immunologic basis and genetic predisposition in some

population groups.[10,11] SJS and TEN are categorised as delayed-type IV hypersensitivity reactions with a typical latency period of between 4-28 days.[12] It is postulated that CD8+ cytotoxic T-cells and natural killer (NK) cells induce apoptosis of the keratinocytes and this occurs as a result of certain mediators which include Fas ligand, perforin and granulysin.[13] These mediators have been the target of possible immunomodulatory agents suggested as treatment options for this condition.[13]

Clinical features

Stevens-Johnson syndrome and TEN begins with the development of a prodrome of flu-like symptoms a few days prior to mucocutaneous lesions occurring.[12] Initially the patients complain of painful, erythematous lesions and blisters developing on the upper aspect of the body and extending over the course of a few days to involve the rest of the body with subsequent epidermal necrosis and denudation.[14,15] Mucous membranes are involved in all cases of SJS and TEN with varying degrees of severity. The oral mucosa followed by ocular surfaces are most commonly involved.[12,14]

Differential diagnosis

The most important condition to differentiate from SJS and TEN is erythema multiforme, which can be delineated by lesion morphology, aetiology, precipitating factors, and systemic involvement. Other conditions that may clinically be considered are generalised bullous fixed drug eruption, certain bullous dermatoses such as pemphigus vulgaris which would need a skin biopsy and direct immunofluorescence for confirmation.[12]

Aetiology and drug causes

The majority of SJS and TEN reactions are secondary to drug exposure while a smaller proportion may be infection related.[16] Infections that are associated with SJS and TEN development include; human immunodeficiency virus (HIV), *Mycoplasma pneumoniae* infection and less commonly; herpes simplex virus (HSV).[12,15,17] Systemic lupus erythematosus (SLE) presents a unique clinical challenge; with some patients presenting with a rare form of acute cutaneous lupus (TEN-like lupus) and others presenting with SJS or TEN due to an identifiable drug cause but also known with a diagnosis of SLE on medical history.[2] Some case reports have suggested vaccinations and malignancies to be possible causative factors and in the minority an aetiologic factor cannot be identified.[12,13,17,18] Multiple different medications have been identified as triggers for the spectrum of SJS and TEN.[12,16] The most frequently implicated drug classes are antibiotics, anti-gout (allopurinol), anti-epileptics, nonsteroidal anti-inflammatory drugs (NSAIDs) and antiretroviral therapy (ART).[7,16,19] Prescribing preferences, drug availability, genetics and disease profile would impact the variation in causative drug classes across different geographic areas.[4,8,20]

Developed countries

Allopurinol has been identified as a common drug cause in certain developed areas.[4,21] Between 1997 and 2001 a large European case-control study was done to determine drug risk in known offending agents and newer agents. This study classified nevirapine and lamotrigine as new 'high risk drugs', and confirmed allopurinol, trimethoprim-sulfamethoxazole (TMP/SMX) and certain anti-epileptic agents to still be considered in the same 'high risk' category.[16] Recently there has also been an increase in adverse drug reactions involving newer drug agents such as immune checkpoint inhibitors more specifically in the developed countries.[22]

Developing countries

In developing countries, the most common inciting drugs demonstrate some similarities, but differences are also evident when reviewing literature from Africa.[7,20,23] A retrospective study conducted over a 14-year period in Nigeria identified ART, antibiotics, and anti-malarial medication as the most common causes.[23] This is reflective of ARTs and antibiotics being the most common causes in Sub-Saharan Africa. Previous studies from South Africa concluded the same implicated agents.[7,8] In comparison, Abou-Taleb *et al.* identified anticonvulsants as the most common cause, followed by NSAIDs and antibiotics in an Egyptian cohort.[20] This study did not identify ARTs as a causative factor which is consistent with the very low rate of HIV infectivity in Egypt compared to Sub-Saharan Africa.[20,24]

Risk factors

Several patient- and drug- related factors have been associated with an increased risk of SJS and TEN development. Increased age, female sex, malignancy, and HIV-infection are patient-related factors that contribute to the increased risk. Drug-related factors include 'high risk' drugs, drug half-life, dosage and polypharmacy.[12]

Age and gender

Stevens-Johnson syndrome and TEN can occur in any age group but has an increased incidence in the elderly. This increased risk can be attributed to several reasons which include altered drug metabolism, polypharmacy and immunologic changes that may occur with increasing age.[2,25,26] Studies have considered females to be predisposed to SJS and TEN development with a ratio of 2:1[27], this higher female to male ratio correlates with several South African studies.[7,8,28] Contradicting this, a study conducted in Egypt found the inverse to be true, with a male predominance.[20,29] The reasons for gender differences are ill-defined.

Genetics

Multiple studies have confirmed the role of genetics in the development of SJS and TEN.[5,30] Genetic predisposition varies depending on ethnicity and the drug involved. This can be demonstrated by the predisposition in Han-Chinese with HLA-B*1502 positivity and SJS-induced by carbamazepine.[5] A genome-wide association study done in Malawi showed an association between HLA-C*04:01 and predisposition to nevirapine-induced SJS.[30] The feasibility of genetic testing would depend on the prevalence of the specific allele and determining the degree of positivity between the allele and development of SJS and TEN in a population. The development of SJS and TEN is not only dependent on genetics but an interplay of multiple factors.[12,17] Genetic testing in our population would not be economically feasible due to nevirapine not being recommended as a first-line drug in current treatment guidelines.[31] A link between recurrent erythema multiforme and HLA DQB1*0301 has been demonstrated which contrasts with the pharmacogenetic profile implicated in SJS and TEN.[5,11]

HIV

HIV infection is well recognised as an independent risk factor for SJS and TEN development, with literature stating an approximately 1000-fold higher risk compared to the general population.[19] Antiretroviral therapy and certain antibiotics such as TMP/SMX have also been identified as frequently implicated agents for SJS and TEN.[16] The increased risk is due to a multivariable complex interplay between immunologic, genetic, and metabolic factors that increases HIV patient susceptibility to development of SJS and TEN. HIV infection creates a unique environment involving polypharmacy, immune dysregulation, HIV associated malignancies as well as opportunistic infections such as tuberculosis. It is also well established that metabolic changes such as antioxidant deficiency and slow acetylation of drugs contribute to the increased risk.[32] Immunophenotyping of skin biopsies taken from HIV-infected TEN patients demonstrated that there is a decrease in the skin protective regulatory T-cells because of an increased ratio of CD8+ to CD4+ cells compared to noninfected patients.[33]

Determining causality

Identifying the causative drug is challenging and commonly more than one inciting agent may be identified.[21] There is no definite investigation or method of identifying the causative drug, consequently the clinician's experience, judgement and epidemiological data are crucial in assigning causality. The temporality of drug initiation and the onset of the eruption are important factors when determining drug causality. Determining causality in HIV-infected patients becomes more difficult, due to the use of multiple high-risk drugs, concurrent initiation of multiple drugs, higher drug dosages, immune reconstitution syndrome, underlying infections, and malignancy.[8] There are several causality assessment tools that help in establishing implicated drugs.[34,35] The ALDEN (Algorithm of Drug

causality for Epidermal Necrolysis) score was developed to aid in the assessment of drug causality in patients with SJS and TEN.[35] The algorithm considers various parameters, and each potential drug is scored. Parameters include the time delay from initial drug intake to the onset of reaction, whether the implicated drug was present in the body on the index day, drug challenge, re-challenge and de-challenge history. The score then ranks the probability of the drug causing SJS and TEN. This algorithm is mostly used retrospectively but the general principles can be used in the acute clinical setting.[35] The score is calculated based on 6 parameters, for each drug a score is calculated which ranges from -12 to +10. Then categorised based on the total score as: very probable (>6), probable (4-5), possible (2-3), unlikely (0-1), and very unlikely (<0). The ALDEN score (Table 1) is not routinely used at the Department of Dermatology at Universitas Academic Hospital.[35]

Table 1: ALDEN SCORE[35]

Criterion	Values	Rules to apply	Possible value
Delay from initial drug component intake to onset of reaction (index day)	Suggestive +3	From 5 to 28 days	-3 to 3
	Compatible +2	From 29 to 56 days	
	Likely +1	From 1 to 4 days	
	Unlikely -1	> 56 days	
	Excluded -3	Drugs started on or after the index day.	
		In case of previous reaction to the same drug, only changes for: Suggestive: +3: from 1 to 4 days Likely: +1: from 5 to 56 days	
Drug present in the body on index day	Definite 0	Drug continued up to index day or stopped at a time point less than five times the elimination half-life before the index day.	-3 to 0
	Doubtful -1	Drug stopped at a time point prior to the index day by more than five times the elimination half-life but liver or kidney function alterations or suspected drug interactions are present.	
	Excluded -3	Drug stopped at a time point prior to the index day by more than five times the elimination half-life	

		without liver or kidney function alterations or suspected drug interactions.	
Prechallenge/rechallenge	Positive specific for disease and drug: 4	SJS/TEN after use of same drug.	-2 to 4
	Positive specific for disease or drug: 2	SJS/TEN after use of similar drug or other reaction with same drug.	
	Positive unspecific: 1	Other reaction after use of similar drug.	
	Not done/ unknown: 0	No known previous exposure to this drug.	
	Negative -2	Exposure to this drug without any reaction (before or after reaction).	
Dechallenge	Neutral 0	Drug stopped.	-2 to 0
	Negative -2	Drug continued without harm.	
Type of drug (notoriety)	Strongly associated 3	Drug of the “high risk” list according to previous case-control studies.	-1 to 3
	Associated 2	Drug with definite but lower risk according to previous case-control studies.	
	Suspected 1	Several previous reports, ambiguous epidemiology results (drug “under surveillance”).	

	Unknown 0	All other drugs including newly released ones.	
	Not suspected -1	No evidence of association from previous epidemiology study with sufficient number of exposed controls.	
		Intermediate score = total of all previous criteria.	-11 to 10
Other cause	Possible -1	Rank all drugs from the highest to lowest intermediate score	-1
		If at least one has an intermediate score >3, subtract 1 point from the score of each of the other drugs taken by the patient (another cause is more likely).	

Final score -12 to 10

Complications

Even though SJS and TEN are considered rare, they contribute to a large proportion of morbidity and mortality in dermatology patients worldwide.[27] The most common cause of mortality in this population group is sepsis.[6,14] Due to a weakened skin barrier patients with SJS and TEN are at increased risk of infection and subsequent sepsis. The extensive sloughing of the epidermis results in large amounts of fluid and protein loss and this has been compared to burn wound patients.[6] Additionally, short- and long-term multisystem morbidity may occur, this includes renal, pulmonary, ophthalmologic and gastrointestinal complications.[14] A retrospective study conducted in the United States, concluded that nearly half of the study cohort had long-term complications which ranged from most commonly ocular involvement to lung and gastrointestinal sequelae.[36] South African studies have generally not focused on the long-term sequelae related to SJS and TEN, most have concentrated on immediate outcome and mortality.[7-9]

An additional risk for infectious complications in SJS and TEN is the risk of indwelling line infections. Placement of peripheral lines is challenging in these patients, often requiring central venous line placement. Application to occlusive dressing to these lines may also be problematic depending on the extent of the skin involvement. The most common micro-organisms cultured in these patients are *Staphylococcus aureus* and *Pseudomonas aeruginosa.*[9]

Ocular complications can develop early on in the disease process with resultant debilitating long-term sequelae if there is no ophthalmologic intervention.[14,15] Severe complications include symblepharon formation and corneal ulceration with the possibility of resultant loss of vision.[14]

Genital mucosal complications can occur in both genders. Males may complicate with urethral strictures as a sequela. In females an important aspect of management is care of the vulvovaginal mucosa. Stevens-Johnson syndrome and TEN may lead to the development of bleeding, vaginal adhesions and dyspareunia.[14] These complications can lead to further anatomic and reproductive challenges.

Other complications commonly occurring include electrolyte abnormalities, renal impairment, which may necessitate dialysis, due to large fluid losses and a hepatitis.[12] Systemic complications may include pulmonary (chronic bronchitis) and genitourinary (strictures, adhesions) systems. These conditions have an impact on the physical, social and psychological well-being of these patients.[14]

Due to underlying genetic predisposition to severe drug reactions, patients with SJS and TEN have a life-long predisposition to recurrence. Recurrence may occur if the person is re-exposed to the implicated drug or other aetiological agents. Due to prior sensitisation, the latency period will be shortened.[14]

Mortality

The overall estimated mortality is between 20-25% in patients with SJS and TEN, this reflects studies conducted in Europe.[27] A validated scoring system that helps assess disease severity and predict mortality in patients with SJS and TEN; SCORTEN (severity-of-illness score for toxic epidermal necrolysis) can be calculated on day 1 and 3 of hospitalisation. The SCORTEN is calculated based on seven independent parameters each receiving 1 point: Age > 40-years, heart rate > 120 beats per minute, presence of malignancy, involved TBSA > 10%, serum urea > 10mmol/L, serum bicarbonate < 20mmol/L and blood glucose > 14mmol/L. This score correlates with a percentage of predicted mortality (*Table 2*)[37] There exists some limitations with this prognostic scoring system such as confusion regarding when the SCORTEN should be calculated for highest accuracy, with studies

suggesting day 1 and 3 while others suggest day 5.[38] Additionally, some studies have highlighted deficiencies in the SCORTEN and have suggested modification of the parameters to improve disease prognostication.[27,38] A prospective study conducted in India suggested the importance of other comorbidities besides malignancy having an effect on mortality, with the significance of systemic diseases related to geographic area.[38] A retrospective review by Imahara *et al.*, concluded that in a setting with a standardised treatment protocol SCORTEN overestimated mortality by 33%.[39] It has been recommended that other systemic diseases should be added to the variables including tuberculosis, diabetes mellitus and other chronic conditions. Modifications to the SCORTEN have been suggested due to population differences, varying treatment protocols as well as HIV-infection status.[38]

Table 2: **SCORTEN score for SJS/TEN**[37]

Variable	**SCORE**
Age above 40 years	1
Heart rate above 120 bpm	1
Malignancy	1
Initial skin detachment > 10% BSA	1
Serum urea > 10mmol/L	1
Serum bicarbonate < 20mmol/L	1
Blood glucose > 14mmol/L	1
SCORTEN score	**Mortality (%)**
0-1	3
2	12
3	35
4	58
>5	90

bpm: beats per minute; BSA: body surface area; SCORTEN: score of epidermal necrolysis; SJS: Stevens Johnson syndrome; TEN: toxic epidermal necrolysis

Treatment

Management involves cessation of the suspected drug(s) and supportive care.[40] Early withdrawal of the suspected drug has shown a better prognostic outcome, while some drugs with long half-lives correlate with increased morbidity.[40]

Supportive care

Improved outcomes have been shown following expeditious transfer to and management in a burn or intensive care unit (ICU).[15,41] This is not routinely possible in resource-limited settings, such as ours.

Supportive care forms the mainstay of treatment which includes; thermoregulation, adequate fluid and electrolyte management, analgesia, wound care, infection surveillance, nutritional support, pain control and anti-coagulants (if indicated).[14,15,52] Early involvement of the multidisciplinary team including ophthalmology, dietetics and internal medicine as required.

Wound care forms an important component of supportive treatment for re-epithelialisation and infection prevention.[15] No standardised guidelines have been developed for wound care in this patient population group, with general principles of using non-adherent dressings forming the mainstay of treatment.[14,15] Antibiotics should only be prescribed when confirmatory microbiological evidence or clinical signs in keeping with infection are present.[15]

Ocular care encompasses early ophthalmologic consultation with prescription of tear replacement, pseudomembrane removal and prevention of scar formation with corticosteroid drops.[15]

Debate continues regarding the adjuvant use of disease-modifying agents such as; systemic corticosteroids, cyclosporine, intravenous immunoglobulins (IVIG) and more recently, tumour necrosis factor-alpha (TNF α) inhibitors.[15,42] In patients with HIV the use of immunomodulating therapies and which specific agent to use is even more challenging. Each patient should be assessed individually when deciding on the use of immunomodulating agents in the context of HIV. Factors to consider would be CD4 count, active tuberculosis infection, and renal function specifically when selecting cyclosporine. [8,10]

Cyclosporine: a calcineurin inhibitor has emerged as a possible immunomodulatory agent with improved outcomes in patients with SJS and TEN. A recent retrospective analysis showed a shorter duration in terminating new lesion development and shorter time to re-epithelisation than those treated with systemic corticosteroids.[43]

The use of systemic corticosteroids is debatable with concerns related to increased risk of infection due to a suppressed immune response and delayed healing.[8] This is especially concerning in a HIV-infected population with an increased risk of opportunistic infections. A study by Mayosi *et al.* showed that in HIV-infected patients steroid use has been associated with an increased risk of HIV-related malignancy, but no significant effect on mortality.[44]

Intravenous immunoglobulins (IVIG) is most often the first adjunctive agent employed in treatment of SJS and TEN due to it inhibiting keratinocyte apoptosis. Multiple studies have been conducted investigating the efficacy of IVIG for the treatment of SJS and TEN with varying outcomes.[45,46] A

retrospective analysis of 64 patients diagnosed with either SJS/TEN overlap or TEN and treated with IVIG showed no reduction in mortality.[46] A multi-centre European study retrospectively reviewed 48 cases of TEN treated with high dose IVIG (1g/kg per day) and concluded a beneficial outcome on patient mortality.[45] Other studies have suggested a better outcome when combining immunomodulatory agents.[8,10,47,48] A recent retrospective study in South Africa involving 36 HIV-infected patients treated with a combination of systemic steroids and IVIG showed a survival rate of 97%.[8] A limitation to the routine use of IVIG in the public health care setting is cost as well as availability.

Further studies are needed to determine the superiority of one immunomodulatory agent over another, though these studies are difficult to conduct due to the rarity of SJS and TEN.

Follow up care

Follow-up care is an often-neglected component of treatment. Studies have shown that patients may manifest with later complications, weeks to months after recovery. This occurs especially in the elderly.[27] The long-term complications have a significant impact on the quality of life.[14]

Aims, Objectives and hypothesis

The aim of the study is to describe the clinical profile, aetiology and implicated drugs, complications, and outcome in patients with SJS/TEN at Universitas Academic Hospital (UAH). Identifying frequently implicated drugs and patients at higher risk of poor outcomes is important in our context. This research will also provide insight into the limitations in our setting, this includes a lack of treatment guidelines, data and deficiency in employing the SCORTEN and ALDEN scoring systems.

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Chapter 2

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Stevens-Johnson syndrome and toxic epidermal necrolysis at Universitas Academic Hospital: A 4-year review

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Abstract

Background

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, life-threatening dermatologic conditions that are part of the same disease spectrum. Drugs are the main inciting factor of this delayed hypersensitivity reaction which produces epidermal and mucosal detachment. Morbidity and mortality is high. Limited data are available on SJS and TEN in our setting.

Aim

We aimed to characterise patient demographics, aetiology and implicated drugs, treatment and outcome in patients with SJS and TEN at a tertiary academic hospital in the Free State, South Africa.

Methods

A retrospective, cross-sectional descriptive single centre study which included participants managed at Universitas Academic Hospital between 2016 and 2020 was performed.

Results

Fifty-five cases meeting the inclusion and exclusion criteria were included in this study. The mean age of the cohort was 37-years (range: 21- 67). The prevalence of HIV was high (38/53; 71.7%%). and a causative drug was identified in most (50/55; 90.9%) cases. Antibiotics (29/50; 58.0%) and antiretroviral therapy (15/50; 30.0%) were the most common drug classes implicated, with trimethoprim-sulfamethoxazole (12/50; 24.0%) and nevirapine (9/50; 18.0%) being identified as the most commonly implicated drugs. The major complication in the cohort was sepsis (23/55; 41.8%). Supportive care formed the mainstay of treatment (42/55; 76.4%) and the mortality rate was 14.5% (8/55).

Conclusion

A high prevalence of HIV infection was noted in this cohort. Nevirapine and trimethoprim-sulfamethoxazole were the most commonly implicated drugs. In resource-limited settings such

as our facility, supportive care forms the predominant feature of treatment with a relatively good outcome.

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, life-threatening dermatologic conditions that are most commonly induced by drugs and less commonly, secondary to some infections.[1] Both SJS and TEN are considered severe cutaneous adverse reactions (SCAR) and result in epidermal necrosis with subsequent epidermal detachment and mucosal erosions of varying severity.[1]

Stevens-Johnson syndrome and TEN are considered variants on the same disease spectrum distinguished by total body surface area (TBSA) involved and are delineated from erythema multiforme by lesion morphology, precipitating factors, and systemic involvement.[1] Patients with SJS and TEN initially develop a prodrome of flu-like symptoms and later manifest blistering cutaneous lesions which evolves to skin necrosis and denudation.[1] By consensus definition; SJS encompasses skin detachment of 10% or less, SJS-TEN overlap between 10% - 30% and TEN more than 30% of the TBSA with all categories having 2 or more mucous membranes involved.[2] The term SJS and TEN will be used to collectively refer to SJS, SJS-TEN overlap and TEN.

Stevens-Johnson syndrome is reported to be more common than TEN with an estimated incidence of approximately 1 - 6 cases per million persons per year and that of TEN is estimated to be 0.4 - 1.2 cases per million persons per year.[3-5] The prevalence and incidence differs substantially between countries and is contingent on various factors such as genetic predisposition, prescribing preferences and drug availability.[6,7]

The risk of SJS and TEN is increased based on certain patient- and drug-related factors. An increased incidence has been reported in patients with advanced age, female sex and malignancy. HIV infection is considered to be an independent risk factor.[8,9]

Numerous drugs have been associated with SJS and TEN.[10] South African literature suggests that the most commonly implicated drugs are nevirapine and trimethoprim-sulfamethoxazole (TMP-SMX).[11,12] Even though SJS and TEN are considered rare, they contribute to a large

proportion of morbidity and mortality in dermatology patients worldwide, with sepsis being the most common cause of mortality.[13] Additionally, short- and long-term multisystem morbidity may occur, this includes sepsis, pulmonary, ophthalmologic and gastrointestinal complications.[13] The estimated mortality is between 10% and 50% for SJS and TEN respectively, with these studies mainly being conducted in the European setting.[14,15]

Management of SJS and TEN involves cessation of the suspected implicated drug(s) and supportive care.[15] Improved outcomes have been shown following expeditious transfer to and management in a burn or intensive care unit (ICU).[16,17] There are no standardised treatment protocols for SJS and TEN, however, pharmacologic agents such as cyclosporine, intravenous immunoglobulins (IVIG), and systemic corticosteroids have been proposed with varying outcomes.[18,19]

To date, no country-wide studies have been performed to investigate the epidemiology and outcome of patients with SJS and TEN in South Africa. Furthermore, the studies that have been conducted in South Africa are not comparable as they have had different study designs.[11,12,20,21] Overall, this highlights the paucity of country-wide epidemiologic studies which would contribute to the available data and possibly identify areas of uncertainty that need more investigation and active intervention. According to the researchers' knowledge, no other published studies on SJS and TEN have been conducted in the Free State province of South Africa.

The aim of this study is to retrospectively review and characterise the clinical profile, causative agents, treatment and outcomes of patients at a tertiary hospital in the Free State province of South Africa.

Methods

Study design

A retrospective cross-sectional study among patients admitted with SJS, SJS-TEN overlap and TEN at Universitas Academic Hospital (UAH) in Bloemfontein, South Africa was performed.

SETTING

Universitas Academic Hospital is a 636-bed tertiary referral hospital with a Dermatology Department. The Department of Dermatology has an 8-bed ward where most patients with SJS and TEN in Free State province and some from Lesotho, a neighbouring country, are admitted.

PARTICIPANTS

All patients admitted to and treated at the Department of Dermatology at UAH between 1 May 2016 and 30 April 2020 were included in the study. Consultants or dermatology registrars clinically assessed and confirmed the diagnosis of SJS and TEN according to the validated consensus criteria laid down by Bastuji-Garin *et al.* as standard practice (*Table 1*).[2]

Table 1: Classification for EM/SJS/TEN

Classification	Bullous EM	SJS	Overlap SJS-TEN	TEN with spots	TEN without spots
Detachment (% body surface area)	<10%	<10%	10%-30%	>30%	>10%
Typical targets	Yes	No	No	No	No
Atypical targets	Raised	Flat	Flat	Flat	No
Spots	No	Yes	Yes	Yes	No

EM: Erythema multiforme; SJS: Stevens-Johnson syndrome; TEN: Toxic epidermal necrolysis

All patients with the International Classification of Diseases (ICD)-10 codes: L51.1, L51.2 and L51.3 (SJS, SJS-TEN overlap and TEN respectively) were screened for eligibility. The ICD-10 code T88.7 for unspecified adverse effects of drug or medicament was additionally included to ensure that no patients were missed due to misclassification. Patients younger than 18 years of age and those diagnosed with other adverse drug reactions as a final diagnosis were excluded.

DATA SOURCES/MEASUREMENT

The hospital administrative electronic database, Meditech (MEDITECH South Africa (Pty) Ltd.) was searched using the included ICD-10 codes to identify potential participants. Medical records of all the potential participants were retrieved and manually reviewed by the primary investigator to confirm whether they met the inclusion and exclusion criteria. Other data were obtained from National Health Laboratory Service (NHLS) Trakcare (Intersystems, USA) laboratory results portal, nursing observation charts and clinical notes. Drug causality was assigned based on the clinicians' judgement, the temporality of drug initiation, the onset of symptoms, and detailed patient medication history as documented in the clinical notes.

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of the Free State. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages, and 4) procedures for data integration and interoperability with external sources.[22,23]

VARIABLES

An electronic REDCap data sheet was developed and populated with the following information: patient demographics (sex and age), diagnosis (based on the percentage of TBSA), implicated drug(s) taken within 4-8 weeks of the onset of symptoms, the period between the drug intake and the appearance of symptoms, comorbid medical conditions, HIV status (CD4 count if positive), laboratory parameters, associated complications, treatment, morbidity and mortality.

STATISTICAL METHODS

Data were exported onto Microsoft Excel 2021 (Microsoft Corporation, USA) and provided to the Department of Biostatistics at the University of the Free State, who performed the data analysis using Statistical Analysis Software (SAS version 9.4), (SAS Institute Inc., Cary, NC, USA). Numerical data were expressed as medians and interquartile ranges (IQR). Categorical data were expressed as percentages and compared using the Chi-Square or Fisher's Exact Test. The level of statistical significance was set at a p-value < 0.05.

Ethical considerations

Ethical approval for the study was obtained from the Health Sciences Research Ethics Committee (HSREC) of the University of the Free State (ref number: UFS-HSD2020/1247/2909-0001). Permission was granted from NHLS for the use of laboratory data and the Free State Department of Health approved this study. All collected data were de-identified.

Pilot study

A pilot study that included five non-consecutive, randomly selected participants was performed. It was noted that it was not possible to obtain the variables required to calculate the SCORTEN score, as serum bicarbonate was not routinely performed. The challenge of obtaining the parameters needed for the SCORTEN score has been noted by others.[20,24]

A protocol amendment was submitted and calculation of the SCORTEN score was removed as an objective.

Results

Participants

Sixty files were identified using the search strategy described above. Five patients did not meet the inclusion criteria and were excluded (figure 1). Fifty-five participants met the inclusion criteria.

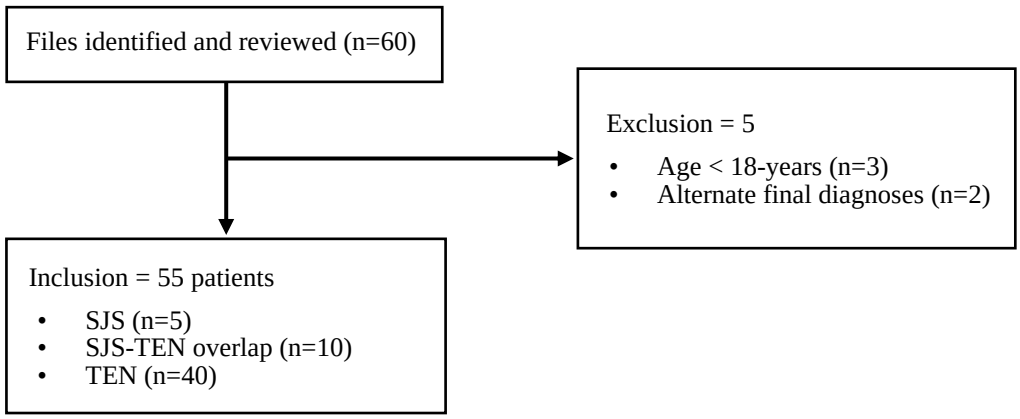

Figure 1: Participant selection process

Demographic data

A male predominance (32/55; 58.2%) with a male to female ratio of 0.71 was noted. The median age was 37 years (range 21 – 67 years). The majority of participants were diagnosed with TEN (40/55; 72.7%), followed by SJS/TEN overlap (10/55; 18.2%) and a minority with SJS (5/55; 9.1%). No statistically significant differences were noted between the mean ages according to diagnostic classification.

Aetiology

An identifiable causative drug was found in most (50/55; 90.9%) participants of the cohort, and in the minority of cases (4/55; 7.3%) no cause could be identified. One participant developed SJS/TEN secondary to confirmed *Mycoplasma pneumonia* infection. Amongst participants with an identified drug cause many (23/50; 41.8%) had more than one possible causative drug identified. Multiple drug categories were identified as causes in this study with the most common class being antibiotics (29/50; 58.0%) followed by antiretroviral agents (15/50; 30.0%). Trimethoprim-sulfamethoxazole (12/50; 24.0%) and nevirapine (9/50; 18.0%) were identified as the most commonly implicated drugs. Six females and three males were using nevirapine at time of diagnosis. *Table 1* specifies the causative drugs involved.

Latency period

The majority of the cohort (37/50; 74.0% had a latency period from drug initiation to drug reaction of between 5 - 28 days. A minority of patients developed symptoms beyond 29 days and within 4 days of drug initiation (5/50; 10.0% and 1/50; 2.0% respectively). Some patients had an unknown duration of medication use (7/50; 14.0%). Drug causality was mainly categorised as ‘very probable’ (35/50; 70.0%) with the remainder ‘probable’ (15/50; 30.0%) according to the ALDEN (Algorithm of Drug causality in Epidermal Necrolysis) score.[25]

Table 1: Drugs implicated in the study population

Drug		total n	% of total
Antibiotics		29	58.0
Sulpha related compounds			
Sulfamethoxazole-trimethoprim	12		
Anti-TB drugs			
RH/INH/PZA/ETH	7		
INH only	4		
Other			
Penicillin	5		
Metronidazole	1		
Antifungals		1	2.0
Antivirals		15	27.3
Nevirapine	9		
Efavirenz	1		
TDF/ETC/EFV combination	5		
Anticonvulsants		10	18.2
Phenytoin	6		
Carbamazepine	2		
Valproic acid	1		
Lamotrigine	1		
NSAIDs		5	9.1
Ibuprofen	5		
Gout		2	3.6
Allopurinol	2		
Complimentary medicine		2	3.6
Traditional/herbal medication	2		

TB: Tuberculosis; RH: Rifampicin; INH: Isoniazid; PZA: Pyrazinamide; ETH: Ethambutol;

TDF: Tenofovir; ETC: Emtricitabine; EFV: Efavirenz; NSAIDs: non-steroidal anti-inflammatory drugs

CLINICAL PROFILE AND COMORBIDITIES

The HIV infection status of most participants (52/55; 94.55%) was known. One participant with an unknown HIV infection status had nevirapine documented as the implicated drug, inferring HIV infection. Thus, the prevalence of HIV in the cohort was high (38/53; 71.7%%). The differences in the HIV infection rate between the 3 groups of SJS and TEN showed no statistical difference (p=0.8086). Almost two-thirds of the HIV-infected participants (24/38; 63.2%) were classified according to the World Health Organization (WHO) [26] as stage 4 HIV (CD4 < 200 cells/mm^3) and of those, half (12/24; 50.0%) had a CD4 count of less than 50 cells/mm^3. Most participants (28/38; 73.7%) were taking anti-retroviral therapy (ART) at the time of admission. HIV viral load (VL) was performed on eight participants at or within 6-months preceding presentation with SJS and TEN. Virological suppression (defined as HIV VL < 1000 copies/mL) was reported in half of these participants (4/8; 50%). The participants who were HIV-infected but not on ART (10/38; 26.3%) were considered to be virally unsuppressed. *Table 2* summarises the HIV-related information of the study cohort.

Table 2: HIV-related data of study cohort

	n (%)
HIV positive	38
Not taking ART	10 (26.3)
Taking ART	28 (73.7)
Viral load	
Viral suppression*	4 (14.2)
Unsuppressed	4 (14.2)
Not done**	20 (71.4)
CD4 count (cells/mm^3)	
>500	4 (10.5)
350-500	2 (5.3)
200-350	6 (15.8)
<200	24 (63.2)
50-200	12
<50	12
Unknown	2 (5.30)

HIV: Human immunodeficiency virus; ART: Antiretroviral therapy; CD4: Cluster differentiation 4; *taken as a documented laboratory result with viral copies of less than 1000/ml; **No documented evidence of a viral load taken in within preceding 6 months

The majority (32/54; 59.3%) of the cohort had an associated comorbidity other than HIV infection at the time of admission. HIV-infection was the only co-morbidity in 17 participants, five participants had neither HIV nor a comorbidity and one did not have data on comorbidities. None of the participants had an underlying malignancy. A few participants (6/33; 18.2%) were

being treated for active tuberculosis. Other comorbidities included cardiometabolic disease, infections, haematologic, neuropsychiatric disorders and others as summarised in *figure 2*. No participants were pregnant at the time of diagnosis. The mean haemoglobin (Hb) on admission was 12.4 g/dL (range 6.8 - 16.5 g/dL). Anaemia was defined according to WHO criteria for men and women as Hb < 13 and <12g/dL, respectively.[27] Almost half (25/54; 46.3%) of the participants for whom baseline haemoglobin results were available were anaemic. Anaemia was more prevalent in the male population (15/31; 48.4% and 9/23; 39.1% for males and females respectively).

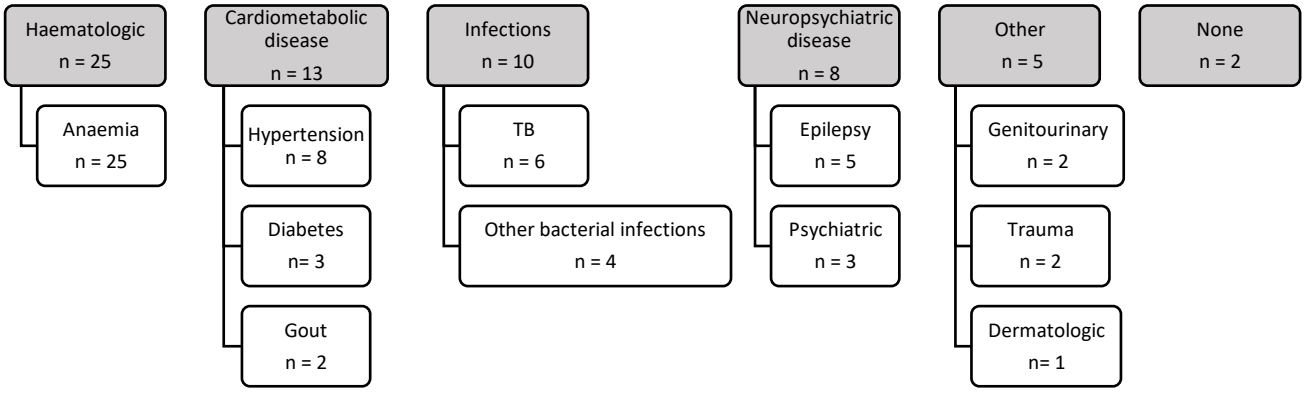

Figure 2: Comorbidities in the study population

The median TBSA of participants was 50% (range: 10 – 90%; IQR 25 – 70%). All participants had mucosal involvement of the ocular, oral or genital area.

TREATMENT

According to institutional practice, all participants admitted received supportive care comprising cessation of the suspected culprit drug(s), adequate fluid replacement, analgesia, wound dressings, antibiotics (if indicated), ophthalmic and oral care; this incorporates a multidisciplinary team approach. Multi-disciplinary care included ophthalmology, dietetics and internal medicine consultations as required. The majority of participants received supportive care alone (42/55; 76.4%) with no further immunotherapy. Adjunctive immunotherapy was prescribed in a quarter of the cohort (14/55; 25.5%) in the form of systemic steroids (4/14; 28.6%), intravenous immunoglobulins (IVIG) (9/14; 64.3%) or both (1/14; 7.1%). Immunotherapy agents like TNF-α inhibitors, cyclosporine, or plasmapheresis were not prescribed.

Most (51/55; 92.7%) of the cohort were managed in the general dermatology ward. The minority (5/55; 9.1%) were presented to ICU for admission, with a good acceptance rate (4/5; 80.0%). One participant was not accepted to ICU due to poor prognosis. Half (2/4; 50%) of the participants admitted to ICU required ventilatory support.

Complications

Complications were noted in 32 (58.2%) of the cohort. The most common complication documented was bacteraemia or fungaemia (23/55; 41.8%), followed by acute kidney injury (AKI) (10/55; 18.2%) and drug-induced liver injury (9/55; 16.4%). One participant with AKI required dialysis. Other complications included electrolyte derangements (8/55; 14.5%), mucosal adhesions (5/55; 9.1%), multi-organ failure (4/55; 7.1%), pneumonia (4/55; 7.1%), acute respiratory distress syndrome (ARDS) (2/55; 3.6%) and venous thromboembolism (2/55; 3.6%). Complications were not graded according to severity.

In-hospital outcomes

The mean length of hospitalisation was 11 days, (range 1 – 29). The majority of participants (43/55; 78.2%) who were admitted were discharged home, a few (3/55; 5.5%) were referred to their local hospital for the continuation of supportive care, one requested an early discharge (and signed a refusal of hospital treatment form). The remainder (8/55; 14.5%) demised during their hospital stay (*Table 3*).

Table 3: Mortality in SJS and TEN

Age	Gender	Diagnosis	Implicated drug(s)	BSA (%)	Comorbidities	Adjunctive therapy	Complications
21	F	SJS/TEN overlap	Nevirapine	25	HIV	None	ARDS, Multi-organ failure, electrolyte derangements
38	F	TEN	Griseofulvin	50	HIV	None	ARDS, Pneumonia
58	M	TEN	Phenytoin	90	Epilepsy, anaemia	IVIG	Septic shock, AKI, Multiorgan failure
59	F	TEN	Unknown	50	Hypertension	None	Septic shock, AKI
65	F	TEN	Nevirapine	60	HIV, Anaemia, Schizophrenia	IVIG	Septic shock, AKI, VTE
67	F	SJS/TEN overlap	Allopurinol	25	Previous stroke	None	Septic shock, AKI, electrolyte derangements
39	M	TEN	Allopurinol	60	Diabetes mellitus, hypertension, gout	Corticosteroids, IVIG	Septic shock, AKI, Multiorgan failure
39	M	TEN	Phenytoin	70	HIV, Anaemia, skull fracture	None	Unknown

BSA: Body surface area; SJS: Stevens- Johnson syndrome; TEN: Toxic epidermal necrolysis; HIV: Human immunodeficiency virus; ARDS: Acute Respiratory Distress Syndrome; IVIG: intravenous immunoglobulin (Polygam®); AKI: Acute kidney injury; VTE: Venous thromboembolism.

Discussion

In this retrospective study we analysed the data of 55 participants diagnosed with SJS and TEN in a tertiary hospital over a 4-year period. While other studies have shown a female predominance, our cohort consisted mainly of males (58.2%).[24,28,29] A South African study that included patients with SJS and TEN between 2010 and 2011 noted a disproportionately high

female to male ratio of 8:1, with half of the women being pregnant.[12] This difference may be explained by the change in the HIV treatment guideline which removed nevirapine as treatment in HIV positive pregnant which took effect in 2012.[30] Interestingly, we did not have any pregnant women in our cohort.

Our patient cohort demonstrated more TEN than SJS cases, this is in contrast with reported data.[1,4] The reason for this difference may be that our centre is a tertiary referral centre and less severe cases are managed in regional or district hospitals. This difference could also be explained by the late presentation of cases.

Older age has been characterised as a risk factor for the development of SJS and TEN. Additionally, age older than 40-years has been noted to be an indicator of poorer patient outcomes.[31] In comparison, the median age of our patient cohort was younger than 40-years. This may be due to the higher prevalence of HIV infection in the younger age group with the additional exposure to high-risk drugs; or to the lower life expectancy in the South African population compared to those in other studies.[32]

The prevalence of HIV in our cohort is disproportionately high (38/53; 71.7%%), when compared to the prevalence of HIV in South Africa (19.1%).[33] The reasons for the high prevalence rate in our study can be attributed to HIV infection being an independent risk factor for the development of immune-mediated drug reactions like SJS/TEN.[9,34] There is a multivariable complex interplay between immunologic, genetic and metabolic factors that increases HIV patient susceptibility to the development of SJS and TEN.[34] HIV infection creates a unique environment involving polypharmacy, immune dysregulation, HIV associated malignancies as well as opportunistic infections (e.g. Tuberculosis).[34] It is also well established that metabolic changes such as antioxidant deficiency and slow acetylation of drugs contribute to the increased risk.[34] Immunophenotyping of skin biopsies taken from HIV-infected TEN patients demonstrated that there is a decrease in the skin protective CD4+ CD25+ regulatory T cells as a result of an increased ratio of CD8+ to CD4+ cells compared to noninfected patients.[35] All these factors or a combination thereof would result in an increased risk of developing SJS and TEN.

Drugs implicated in European studies contrast significantly with those from the developing world.[10] Allopurinol was found to be the most common culprit agent identified in a multinational study conducted by Halevy S *et al.*[7] Studies conducted in Africa show some similarities and differences in findings compared to our study. A study performed in Egypt identified anticonvulsants as the most frequent implicated drug class followed by non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics.[36] The reason for these differences may be due to genetic heterogeneity, disease profile and varying prescribing preferences. The HIV prevalence in Egypt is 0.1% of the general population which may explain why ARTs were not commonly implicated drugs in that study.[37] In contrast, a study from Nigeria, where the HIV prevalence is 1.4% among adults (15 – 49 years), concluded ART and antibiotics were the most commonly implicated drug classes, with nevirapine and TMP-SMX being identified as the most frequently implicated drugs.[38,39] This supports the data that HIV infection may be an independent risk factor for SJS and TEN.[9]

Our study showed that the antibiotic agents, of which TMP-SMX was the most commonly implicated drug. The high rate of TMP-SMX use can possibly be attributed to the high proportion of patients being classified as WHO stage 4, with TMP-SMX being used as prophylaxis for opportunistic infections in this population group.[40] In our study, nevirapine, the second most commonly implicated drug in our cohort, was recommended as first-line treatment in pregnant HIV women prior to 2012 due to low cost.[30,41] Nevirapine is well known to be a cause of drug hypersensitivity reactions and the high frequency of nevirapine- induced SJS and TEN in our patient cohort is worrisome and warrants caution when prescribing known high-risk drugs to those at risk, such as HIV-infected patients.[9,42] We hypothesise that prescription of nevirapine might occur due to ART drug shortages at local clinics, which leads to nevirapine being used as a replacement drug, possibly explaining why three of the participants in our cohort were men and none of the women were pregnant. Some of the nevirapine-induced drug reactions could possibly have been avoided if recommendations for prescribing were adhered to.

Consistent with several other studies, we noted a proportion of patients having more than one possible culprit drug being identified and oftentimes a specific drug cannot be identified as the definite agent.[43,44] In our setting, with a high HIV prevalence, determining causality in HIV-infected patients becomes more difficult, due to the use of multiple high-risk drugs, concurrent

initiation of drugs, higher drug dosages, immune reconstitution syndrome, underlying infections, and malignancy.[12]

There are several causality assessment tools that help in establishing implicated drugs.[25,45]An algorithm for Assessment of Drug Causality for SJS and TEN (ALDEN) was developed to help identify the culprit drug in patients with SJS and TEN specifically.[25] This algorithm is mostly used retrospectively but the general principles can be used in the acute clinical setting.[25] These drug causality assessment tools are a guide and have been assessed as lacking reliability and validity.[46]

Genetic predisposition to the development of SJS and TEN has been proven to play a role in certain ethnicities. This is demonstrated by the significant study done by Chung *et al* which identified an association between HLA-B*1502 and carbamazepine-induced SJS in the Han Chinese population.[6] Subsequent studies have suggested that genotyping in this population group before initiating carbamazepine has decreased the incidence of SJS and TEN among the Han Chinese population.[47] For genetic testing to be feasible would depend on the prevalence of the specific allele and determining the degree of positivity between the allele and the development of SJS and TEN. Genetic testing in our population would not be economically feasible due to nevirapine not being recommended as a first-line drug in current treatment guidelines.

The mainstay of treatment in our institution is supportive care which includes; adequate fluid and electrolyte management, wound care with nonadherent petrolatum impregnated dressings, infection surveillance, nutritional support, pain control and anti-coagulants (if indicated). Early involvement of the multidisciplinary team including ophthalmology, dietetics and internal medicine as required. Antibiotics are only prescribed when confirmatory microbiological evidence or clinical signs in keeping with infection are present.[17] This study did not investigate the extent to which supportive care was implemented, antibiotics prescribed and wound dressings used or whether participants received similar care.

Debate continues regarding the adjuvant use of disease-modifying agents; systemic corticosteroids, cyclosporine, intravenous immunoglobulins (IVIG) and more recently, tumour necrosis factor-alpha (TNF α) inhibitors. Previous published studies have failed to adequately

prove better outcomes of one therapy over the other.[17] It should be noted most of these studies are retrospective case series as randomised control studies are difficult to perform due to the rarity of SJS and TEN.

There have been contradictory results with systemic corticosteroid treatment, with some early studies concluding increased infection rate, delayed healing and increased mortality.[48,49] Although there are studies that suggest an overall beneficial outcome; Chateau *et al.* concluded that a combination of systemic corticosteroids and IVIG treatment in conjunction with diligent skin care in HIV-infected SJS and TEN patients had a positive outcome with a 97.2% survival rate, yet this is not practiced at our institution.[12] A favourable outcome was also reported with early systemic corticosteroid use in a retrospective review conducted by Liu *et al.*[50] Cyclosporine has emerged as a beneficial choice with a retrospective analysis of 93 patients showing a decreased length of hospital stay and decreased time to re-epithelialisation.[51] Recommendations from the U.K. guidelines for the management of SJS/TEN published in 2016 concludes that no definite benefit or harm can be established from studies conducted thus far, emphasising the importance of supportive care.[17]

Complications observed in our study reflect results from multiple other studies, identifying infection as the most common complication in this patient group.[3] Some factors have been noted to predict an increased risk of infection and higher mortality in SJS and TEN patients. A retrospective study conducted by Koh H *et al* identified TBSA > 10%, Hb < 10g/dL, and associated cardiovascular disease including hypertension as the main risk factors for sepsis development and increased mortality.[52] The mortality rate in our patient cohort was 14.5%, occurring in the SJS/TEN overlap and TEN group with supportive care being the predominant treatment choice. Comparatively, a retrospective cohort study of HIV-infected patients in South Africa treated with a combination of systemic steroids and IVIg had a survival rate of 97%.[12]

There is conflicting data on the effect of HIV infection on mortality in SJS and TEN.[11,21] Mortality has been shown to be increased in patients co-infected with tuberculosis.[11] Our study identified anti-tuberculosis drugs implicated in 6 reactions and did not show any association between mortality and those co-infected with TB. Interestingly, while the majority of our HIV-infected cohort was categorised as WHO stage 4 HIV, there was no notable association

between CD4 count and mortality. This has previously been reported.[11] The underlying immunologic changes in HIV-infected individuals with SJS and TEN resulting in an increased CD8 to CD4 ratio could explain for this. [35]

Limitations

The limitations of this study include the retrospective design and findings may be limited by the small sample size. The patients analysed in this study may not be completely representative of the general South African population due to a single-centre source, only servicing patients from the public sector. Data entry and information from medical records are not standardised due to different medical practitioners involved in care. Also, observer bias specifically with the possible over or under-estimation of skin detachment could occur. No institutional consensus treatment protocol is available, treatment prescribed is dependent on the individual prescribing physician. Missing data in medical records led to the inability to calculate SCORTEN.

Conclusion

In conclusion this retrospective study showed that HIV is associated with SJS and TEN, while not associated with increased mortality regardless of WHO HIV stage.[26] Nevirapine, despite not being recommended in national guidelines is still used with resultant SJS and TEN. Supportive care administered in a general dermatology ward remains the mainstay of treatment management with good outcomes.

Further multi-centre national studies are needed to address the paucity of data regarding epidemiology and outcomes in patients with SJS and TEN in the South African context. Future research should take into account the dynamic complexities of SJS and TEN and the need for standardised consensus treatment guidelines. It should also be remembered that our population characteristics are unique in terms of genetics and underlying diseases and clinician prescribing practices therefore our management approach would differ from other geographic areas.

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Appendices

A Letter of approval from HSREC-UFS

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

09-Sep-2020

Dear **Dr Fatima Moosa**

Ethics Clearance: **Stevens-Johnson syndrome and toxic epidermal necrolysis at Universitas Academic Hospital: A 4-year review**

Principal Investigator: **Dr Fatima Moosa**

Department: **Dermatology Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2020/1247/2909**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00011992; REC 230408-011; IORG 0010096; FWA 00027947
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B Letter of approval from HOD – Dermatology

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

19 June 2020

The Chair: Health Sciences Research Ethics Committee
Attention: Mrs. M Marais
Block D, Room 104
Francois Retief Building
Faculty of Health Sciences
University of the Free State
Bloemfontein
9301

Dear Dr. SM le Grange

Fatima Moosa (Student number: 2005069782)

Title: Stevens-Johnson syndrome and toxic epidermal necrolysis at Universitas Academic Hospital: A 4-year review

I, Dr Z.S. Mazibuko hereby grant Fatima Moosa permission to conduct the above-mentioned research project. The research will be completed in accordance with myself as Head of Department of Dermatology and Dr. Claire Armour (Barrett) as supervisor of this study.

Yours sincerely

Dr Z. S. Mazibuko
Head Clinical Unit

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C Letter of approval – DOH-FS

health
Department of Health
FREE STATE PROVINCE

21 August 2020

Dr F Moosa
Dept. of Dermatology
UFS

Dear Dr F Moosa

Subject: Stevens-Johnson syndrome and toxic epidermal necrolysis at Universitas Academic Hospital: A 4-year review.

- Please ensure that you read the whole document. Permission is hereby granted for the above – mentioned research on the following conditions:
- Participation in the study must be voluntary
- A written consent by each participant must be obtained.
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of **Universitas Hospital** nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** sibeelatsoir@health.gov.za/ makenamm@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- **Please discuss your study with Institution Manager on commencement for logistical arrangements see 2nd page for contact details.**
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- **As part of feedback you will be required to present your study findings/results at the Free State Provincial health research day.**

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 25/8/2020

Head : Health
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D Letter of approval – NHLS

NATIONAL HEALTH LABORATORY SERVICE

Practice No. 5200296

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UNIVERSITY OF FREE STATE
BLOEMFONTEIN
9301

REQUEST FOR APPROVAL OF LABORATORY RESOURCES FOR ACADEMIC PURPOSES

Date: 06 July 2020

Requestor: Dr. F Moosa

Project Name: **" Stevens- Johnson syndrome and toxic epidermal necrolysis at Universitas Academic Hospital: A 4-year review "**

Dear Dr. Moosa,

Your request for use of laboratory facilities / data is hereby granted under following conditions:

1) That University Ethical Committee approval and approval from the Universitas Hospital management is obtained
2) All laboratory data remain confidential to the patient and doctor (anonymity is maintained)
3) This Office must be notified before any publication of any results / findings are made.
4) NHLS is recognised in all publications
5) That a successful K-Project application be made and relevant NHLS project cost centre be created to utilise testing at NHLS as per your protocol.

May your project be successful.

Regards

NATIONAL HEALTH LABORATORY SERVICE
2020 -07- 0 6
BUSINESS MANAGER
UNIVERSITAS ACADEMIC
LABORATORIES

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E Protocol

Stevens-Johnson syndrome and toxic epidermal necrolysis at Universitas Academic Hospital: A 4-year review

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Abbreviations:

BSA:	Body surface area
CD4:	Cluster of differentiation 4
HSV:	Herpes simplex virus
NSAIDs:	Nonsteroidal anti-inflammatory drugs (NSAIDs)
SCORTEN:	SCORe of Toxic Epidermal Necrolysis
SJS:	Stevens- Johnson syndrome
TBSA:	Total body surface area
TEN:	Toxic epidermal necrolysis
UAH:	Universitas Academic Hospital

Definitions:

Denudation:	Loss of the epidermis (upper layer of skin) (1)
Erythema multiforme:	Acute, self- limiting delayed hypersensitivity reaction most commonly due to herpes simplex virus (2)
SCORTEN:	Severity of illness scale that estimates the risk of death in patients with SJS/TEN using 7 independent variables (3)
Stevens-Johnson syndrome (SJS):	Rare, acute drug- induced potentially fatal skin reaction involving less than 10% body surface area (2)
Stevens-Johnson syndrome-toxic epidermal necrolysis (SJS-TEN):	Rare, acute drug-induced potentially fatal skin reaction involving 10-30% body surface area (2)
Toxic epidermal necrolysis (TEN):	Rare, acute drug- induced potentially fatal skin reaction involving more than 30% body surface area (2)

Summary of protocol in layman's terms

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are uncommon, life threatening skin conditions that can affect a person of any age. SJS and TEN are names used to describe the same condition; SJS is a milder form and TEN is a more severe form of the same condition. When a person develops SJS/TEN, that person usually feels as if they have the flu. Shortly afterwards the person develops a painful rash and blisters. The rash affects the skin, but can also affect the eyes, mouth and private parts. SJS/TEN causes the upper layer of skin to come loose (detach) and results in skin failure. Any medication (prescription or over-the-counter) may cause SJS/TEN, and very rarely SJS/TEN can be caused by an infection. The development of SJS/TEN is not completely understood but it is considered a very intense allergic reaction and the immune system seems to play an important role. Some people may be at increased risk of developing SJS/TEN, this includes; the elderly, women, persons with underlying HIV (human immunodeficiency virus) infection, and some population groups seem to be more prone to the reaction due to their genes. SJS/TEN are considered emergencies, this is because of the skin failure that SJS/TEN causes. When a person has skin failure, that person cannot control their body temperature, and the skin is not able to provide a protective barrier and this causes an increased risk of infection. A person with SJS/TEN also loses a lot of fluid and important salts in the blood, which can cause dehydration and kidney problems.

There is a score that doctors can use to predict whether patients with SJS/TEN will survive, the score is called the SCORTEN score. The SCORTEN score looks at certain measurements and a calculation is made to predict a patient's chance of surviving SJS/TEN.

The purpose of this study is to review the patient files, hospital and laboratory records and charts of all patients with SJS/TEN who have been diagnosed and treated at Universitas Academic Hospital (UAH). The study will include patients admitted from 1 May 2016 to 30 April 2020. The information we will be collecting includes the patient age, sex, diagnosis, drug(s) suspected to have caused SJS/TEN, some relevant blood results, complications that the patient had whilst admitted and the outcome (whether the patient survived or not) of the patients. The study will describe the profile of patients with SJS/TEN that were admitted to UAH, and also the complications and outcome of patients with SJS/TEN who were admitted to UAH. The study will also describe the drugs that are implicated to cause SJS/TEN in the patients who were admitted to UAH.

Only information available in patient files, hospital and laboratory records and charts will be used. As the study is reviewing records, it is not necessary to obtain informed consent from the patients. All information collected will be anonymous. The study will also help the researchers to understand more about SJS/TEN at UAH.

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, life-threatening dermatologic conditions, that are most commonly induced by drugs and less commonly secondary to infections. These reactions are characterised by an initial prodrome of flu-like symptoms with subsequent development of painful, dusky, violaceous skin macules, atypical targetoid lesions and bullae which progress to complete epidermal necrosis with full thickness denudation and mucosal erosions of varying severity[1].

SJS and TEN are considered variants of the same disease spectrum based on total body surface area (TBSA) involved and is delineated from erythema multiforme by lesion morphology, precipitating factors and systemic involvement. By definition; SJS encompasses skin detachment of 10% or less, SJS-TEN overlap between 10% - 30% and TEN more than 30% of the body surface area[2]. The term SJS/TEN will be used to collectively refer to SJS, SJS-TEN overlap and TEN.

The reported worldwide incidence of SJS and TEN is estimated at approximately 1-6 cases per million persons per year and 0.4-1.2 cases per million persons per year respectively. SJS/TEN can affect anyone but is more commonly seen in patients with a genetic predisposition, women, elderly and persons with underlying HIV infection. The reported literature estimates the incidence to be as high as 1-2 per 1000 persons infected with HIV. The reason for the increased risk in immunocompromised patients is not fully understood but is considered multifactorial due to immune dysregulation, polypharmacy, and underlying genetic factors[3,4,5].

The exact pathogenesis of SJS and TEN has not yet been completely elucidated, but the aetiology is immune-mediated with a delayed-type hypersensitivity reaction and a typical latency period of between 4-28 days which results in a cytotoxic reaction against keratinocytes with subsequent widespread apoptosis[1].

More than 200 drugs have been reported to have an association with SJS/TEN development. A multinational European case-control study identified allopurinol, lamotrigine, carbamazepine, antibacterial sulphonamides, nevirapine and oxicam nonsteroidal anti-inflammatory drugs (NSAIDs) as drugs with the highest risk of causing SJS/TEN[6]. Implicated drugs that result in SJS/TEN would vary across different countries and population groups based on disease profile.

A case-series from Tunisia found that antibiotics, and specifically beta-lactam antibiotics, are the main cause of SJS/TEN in that country[7]. However, anti-tuberculous drugs and antiretrovirals, specifically nevirapine, have been commonly implicated in sub-Saharan Africa[8]. This is similar to local data in the HIV-infected population[9]. These data contrasts with drugs commonly implicated in Europe.

Assessing drug causality is essential for patients diagnosed with SJS/TEN as rapidity of diagnosis and discontinuing the culprit agent improves the outcome[10]. When drug causality is evaluated most commonly this is based on the clinician's judgement, temporality of drug initiation and detailed patient history. The ALDEN (Algorithm of drug causality for epidermal necrolysis) score was developed to aid in assessment of drug causality in patients with SJS/TEN. The algorithm considers various parameters and each potential drug is scored. Parameters include the time delay from initial drug intake to onset of reaction, whether drug was present in the body on index day, drug challenge, re-challenge and de-challenge history. The score will then rank the probability of the drug causing SJS/TEN. The ALDEN score, is not routinely used at the Department of Dermatology at Universitas Hospital[11,12].

The estimated mortality associated with these conditions ranges between 5% for SJS and 30% for TEN[3]. The SCORTEN (SCORe of Toxic Epidermal Necrolysis) was developed and validated by Bastuji-Garin *et al* in patients diagnosed with TEN in France[13]. It is calculated based on the following seven variables: age ,heart rate, epidermal detachment > 10% BSA on day 1 of admission, underlying malignancy, serum urea , serum bicarbonate level, serum glucose.

It has been recommended that other systemic diseases should be added to the variables including; tuberculosis, diabetes mellitus and other chronic conditions. Modifications to the SCORTEN have been suggested due to population differences, varying treatment protocols as well as HIV-infection status[14,15].

The most common reasons for mortality is sepsis leading to multi-organ failure. Other acute complications include respiratory, dehydration with electrolyte disturbances and gastrointestinal complications which adds to the morbidity. Patients with SJS/TEN are at risk of developing chronic sequelae in addition to the above-mentioned acute complications. The chronic sequelae include ocular (symblepharon, dry eyes), pulmonary (chronic bronchitis) and genitourinary (strictures, adhesions)[12]. These conditions have an impact on physical, social and psychological well-being of these patients.

Controversy remains with regards to systemic treatment of SJS/TEN due to multiple conflicting recommendations with no unanimous consensus reached. Currently supportive care forms the mainstay of treatment with immediate cessation of the culprit drug being crucial in improving outcome and decreasing morbidity and mortality. Supportive treatment encompasses topical care and very importantly infection prevention[16].

SJS/TEN are considered rare yet they contribute to a large proportion of mortality in dermatology patients worldwide. Studies conducted in South Africa have been limited and are not comparable as they have had different objectives[17,18]. According to the researchers' knowledge no other studies on SJS/TEN have been conducted in the Free State.

Rationale for the study:

The clinical profile of patients, complications, outcome and most commonly implicated drugs causing SJS/TEN have not been described at Universitas Academic Hospital (UAH). Identifying frequently implicated drugs and patients at higher risk of poor outcome is important in our context.

Aim:

The aim of the study is to describe the clinical profile, implicated drugs and prognostic factors in patients with SJS/TEN.

Objectives:

To describe the clinical profile, of patients admitted with SJS/TEN to UAH.

To describe the complications that patients admitted with SJS/TEN develop at UAH

To describe the outcome of patients admitted with SJS/TEN to UAH.

To describe the drugs implicated as the cause of SJS/TEN.

To describe how these factors relate to one another.

Methods

Study design

A cross-sectional retrospective study will be performed

Setting

The study will be performed using data from patient files admitted to UAH. This is a tertiary referral facility with a Dermatology department, where the majority of patients with SJS/TEN from the Free State and some from Lesotho are referred to for management.

Participant selection

All patients who were diagnosed with SJS, SJS-TEN overlap and TEN will be identified using ward admission records as well as a structured search on Meditech (the patient information system used at UAH) for the following ICD-10 codes (L51.1, L51.2 and L51.3). The study will include patient files of patients who were admitted to UAH in the period: 1 May 2016 and 30 April 2020. It is anticipated that there will be approximately 10 eligible patient files per year, 40 patient files in total.

All admitted patients were clinically assessed and diagnosed by the Dermatology registrars or consultants and diagnosis was made according to the criteria laid down by Bastuji-Garin *et al*[2]. This information is recorded in the patient files.

Inclusion criteria:
Admitted to UAH in the study period
Admission diagnoses: SJS, SJS-TEN overlap, TEN (ICD-10 code: L51.1, L51.2 and L51.3.
Age ≥ 18 years

Exclusion criteria:
Patients admitted with an initial diagnosis of SJS, SJS-TEN or TEN, but alternative diagnosis was later made (e.g. erythema multiforme)

Measurement
The primary researcher will collect data using a data form. Data will be obtained from the following sources: patient files (retrieved from hospital records), UAH Meditech records, NHLS laboratory website (Labtrak), nursing observation charts and notes.

Data forms will be used to collect the following: patient demographics (sex and age), diagnosis, implicated drug(s) taken within 4-8 weeks of onset of symptoms, the time period between the drug intake and the appearance of the rash, comorbid medical conditions, HIV status, CD4 count, vital signs, laboratory parameters, associated complications, treatment, morbidity and mortality (see addendum).

All data will be captured by the researcher on a data form and entered onto REDcap (Research Electronic Data Capture) software hosted at the University of the Free State. REDcap is a secure, web-based software platform designed to support data capture for research studies. REDcap provides an intuitive interface for validated data capture, audit trails for tracking data

manipulation and export. All data is password protected and encrypted. Data will be provided to the Department of Biostatistics in MS Excel.

Methodological and measurement errors

Due to the retrospective nature of this study, it is possible that some records may be missing. In addition, clinical notes may be incomplete or illegible. Participants who have incomplete data will be assessed on a case to case basis. If salient data is missing, the participant's data will be excluded from analysis.

The decision to exclude a participant's data from analysis will be made when both the researcher and the supervisor agree that sufficient data was not available despite researchers best efforts to obtain such data. A flow diagram will be prepared which shows the cases included and excluded from the analysis and the reasons for exclusion.

Pilot study:

A pilot study including the first 5 participants from 2017 will be performed. If no changes are made to the data form, the data from these patients will be included into the data set. The results of the pilot study will be assessed by the researcher, the supervisor as well as the biostatistician before further data collection continues.

Data analysis

Data analysis will be performed with the assistance of the Department of Biostatistics. Results will be summarised by frequencies and percentages (categorical variables) and means and standard deviations or percentiles (numerical variables) this will then be presented in table and graph format.

Time schedule

Task	**Time frame**	**Responsibility**
Protocol submission	July 2020	Researcher
Ethics evaluation	July 2020	Ethics committee
Protocol corrections	August 2020	Researcher
Submission to FSDOH	August 2020	Researcher
Data collection	August- September 2020	Researcher
Data analysis	October 2020	Researcher and Department of Biostatistics
Preparation of manuscript	November – December 2020	Researcher and supervisor

Submission for evaluation	December 2020	Supervisor

Budget

Item	**Quantity**	**Cost**	**Total cost**
Printing data sheets	50	R2.50	R 125.00
Stationery	1	R100.00	R 100.00
Proof reading and editing	1	R 2 500.00	R 2 500.00
Total cost			R 2 725.00

The researcher will carry the costs for the study.

Ethical considerations

The protocol will be submitted to the Health Sciences Research Ethics Committee (HSREC) of the University of the Free State for their consideration and approval. Following approval from the HSREC, the researcher will apply to the Free State Department of Health for their approval. Permission will be obtained from the Laboratory Manager of the National Health Laboratory Service (NHLS) for use of laboratory data. As this is a retrospective analysis of patient charts no informed consent is required from the patients and all intended data to be collected will not reveal any identifying information.

Each patient will be allocated a study number and no identifying information will be collected.

Publication of findings

The data will be submitted to a local or international peer reviewed journal with the goal of publication.

References:

1. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. J Am Acad Dermatol. 2013;69(2):173.e1-173.e13. Available from: http://dx.doi.org/10.1016/j.jaad.2013.05.003
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   Med. 2019;20(1):1–8.
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12. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part II. Prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. J Am Acad Dermatol
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F Data Sheet

Confidential

Data sheet

Record ID	_____
Sex	◯ Male ◯ Female ◯ Unknown
Date of birth	_____
Date of admission	_____
Was a causative drug (of any attributable risk) identified?	◯ Yes a single drug identified ◯ Yes, more than one possible causative drug identified ◯ No ◯ Not documented
Which group does the precipitating therapeutic agent(s) fall into? More than one option may be selected if appropriate.	☐ Sulpha antibiotics (e.g. Co-trimoxazole) ☐ Antibiotic ☐ Antifungal ☐ Combination anti-tuberculosis treatment ☐ INH (isoniazid) monotherpay ☐ Anticonvulsants ☐ Antiretroviral ☐ NSAIDS ☐ Allopurinol ☐ Traditional, complementary or alternative medication ☐ Unknown
Name the most likely causative drug(s).	_____
Duration on causative drug (days)	◯ Drug started on index day ◯ 1 - 4 days ◯ 5 - 28 days ◯ 29 - 56 days ◯ > 56 days ◯ Unknown
Attributable risk	◯ Doubtful ◯ Possible ◯ Probable ◯ Highly probable ◯ Unknown
HIV status	◯ Positive ◯ Negative ◯ Unknown

Is the patient on antiretroviral therapy?	◯ Yes ◯ No ◯ Unknown
What is the CD4 count? Please only provide an answer if the test was performed in the preceding 6 months.	◯ < 50 ◯ 50 - 199 ◯ 200 - 249 ◯ 250 - 349 ◯ 349 - 400 ◯ > 500 ◯ Unknown
Does the patient have a suppressed viral load (< 1000 copies/mL) Please only provide an answer if test performed in the last 6 months.	◯ Yes ◯ No ◯ Unknown
Known underlying malignancy	◯ Yes ◯ No ◯ Not reported
Comorbidities	◯ Tuberculosis ◯ Diabetes ◯ Hypertension ◯ Ischaemic heart disease ◯ Epilepsy ◯ Gout ◯ SLE ◯ Pregnant/postpartum ◯ Other ◯ None
Please list other comorbidities	_____
Haemoglobin at admission	_____
Surface of epidermal detachment at admission (%)	_____

Progress

What besides general supportive treatment, what adjunct therapies did the patient receive? More than one option may be selected if appropriate.	◯ Systemic corticosteroids ◯ Invtravenous immunoglobulin ◯ Cyclosporine ◯ Tumour nectrosis factor inhibitors ◯ Plasmaphaeresis ◯ None of the above
Was patient ever admitted to the ICU/high care/burns unit?	◯ Yes ◯ No, not presented to ICU/high care/burns unit ◯ No, presented to ICU/high care/burns unit but unit declined admission ◯ Unknown

Complications during admission	◯ Bacteraemia/fungaemia ◯ Acute respiratory distress syndrome ◯ Acute kidney injury ◯ Multi-organ failure ◯ Venous thromboembolic disease ◯ Pneumonia ◯ Gastro-intestinal complications ◯ None ◯ Other ◯ unknown
Please describe other complications during admission	_____
Did the patient require intubation and ventilation?	◯ Yes ◯ No ◯ Unknown
Did the patient require haemodialysis for acute kidney injury?	◯ Yes ◯ No ◯ Unknown
Outcome	◯ Discharged from hospital ◯ Deceased ◯ Unknown
Date of outcome (death or discharge)	_____

G Journal author guidelines

AFRICAN JOURNAL OF PRIMARY HEALTH CARE & FAMILY MEDICINE

Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of six paragraphs labelled Background, Aim, Setting, Methods, Results and Conclusion.

- Background: Summarise the social value (importance, relevance) and scientific value (knowledge gap) that your study addresses.
- Aim: State the overall aim of the study.
- Setting: State the setting for the study.
- Methods: Clearly express the basic design of the study, and name or briefly describe the methods used without going into excessive detail.
- Results: State the main findings.
- Conclusion: State your conclusion and any key implications or recommendations.

Do not cite references and do not use abbreviations excessively in the abstract.

Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by the use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic and should clarify the knowledge gap that this study will address. Your argument should be supported by the use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design: This must address the following:

- Study design: An outline of the type of study design.
- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.

- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.
- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used or steps followed in qualitative data analysis.

Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution's name and permit numbers should be stated here.

Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the **SI convention** and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

Conclusion: Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal*

relationship(s) that may have inappropriately influenced them in writing this article. Read our **policy on competing interests**.

- Author contributions: All authors must meet the criteria for authorship as outlined in the **authorship** policy and **author contribution** statement policies.
- Funding: Provide information on funding if relevant
- Data availability: All research articles are encouraged to have a data availability statement.
- Disclaimer: A statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.

Original Research Articles

An original research article presents innovative research within the focus and scope of the journal, according to a clear and well-structured format. Detailed instructions are given below on the structure and contents required. The introduction should argue for the social and scientific value of the research and end with the aim and objectives of the study. Any conceptual or theoretical framework can also be included in the introduction. The methods section should be structured according to the following sub-headings: study design, setting, study population and sampling strategy, intervention (if appropriate), data collection, and data analysis. Occasionally a different structure may be required, for example, in quality improvement or participatory action research. The methods should be followed by a section on ethical considerations. After this, the results are presented. The article should end with a discussion section that summarises the key findings, and then discusses these findings, the strengths and limitations of the study, and any implications or recommendations. This should be followed by a conclusion, acknowledgements and references sections.

Word limit	3500-7000 words (excluding the structured abstract and references)
Structured abstract	250 words to cover a Background, Aim, Setting, Methods, Results and Conclusion
References	60 or less
Tables/Figures	no more than 7 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate
Language	only manuscripts presented in English or French will be considered

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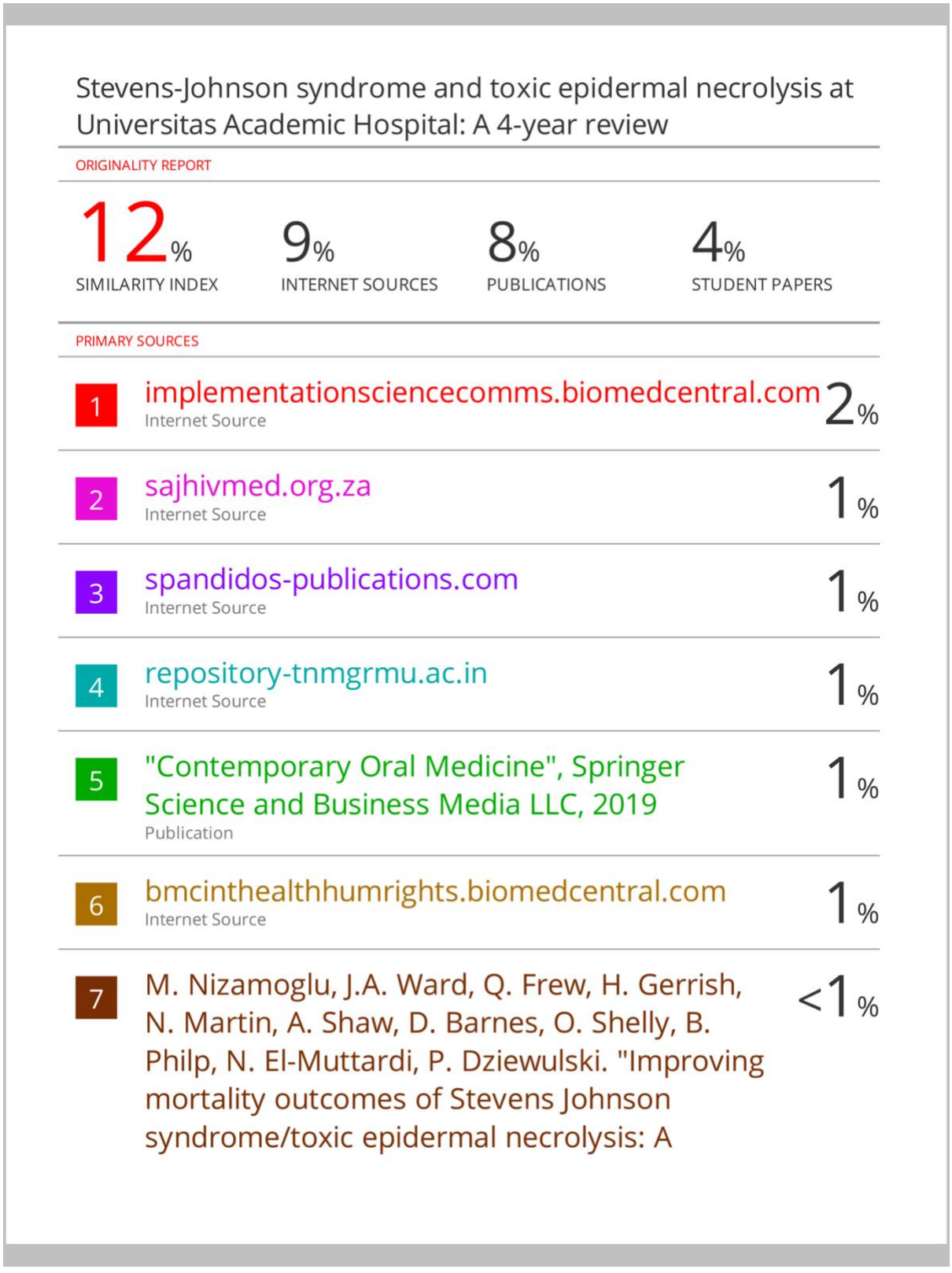

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